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In Vivo Intravascular Laser Photodynamic Therapy in Rabbit Atherosclerotic Lesions Using a Lateral Direction Fiber

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Background and Objective: **This study was performed to evaluate the possibility of inducing regression of atherosclerotic foci by photodynamic therapy (PDT) using hematoporphyrin derivative (HpD).**
Study Design/Materials and Methods: **Atherosclerotic rabbits were divided into four groups. Groups A (n = 6) and C (n = 6) were given 5 mg/kg of HpD intravenously; Groups B (n = 4) and D (n = 4) were not. Twenty-four hours after HpD administration, the aortae of groups A and B were exposed to 200 mw output argon dye laser beam at 630 nm for 10 minutes; groups C and D were exposed to 400 mw for 5 minutes. Three rabbits from groups A and C and two rabbits from groups B and D were sacrificed immediately after laser photoradiation, being named groups A 0, C 0 and groups B 0, D 0, respectively. Groups A 7, C 7 and Groups B 7, D 7 were sacrificed 7 days after the photoradiation.**
Results: **In groups A 7 and C 7, most intimal cells and endothelial cells had become necrotic and disappeared, and a loss of intima was observed. No such changes were found in groups B 7, D 7.**
Conclusion: **The above data suggest that PDT caused effective regression of the atherosclerotic lesions. Lasers Surg. Med. 20: 373–381, 1997.**

Key words: atherosclerosis; argon-dye laser; hematoporphyrin derivative

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA), which dilates the vascular lumen mechanically by inflating a balloon at a stenotic portions of coronary arteries, is widely used to treat atherosclerotic changes. However, this technique entails a high rate of complications such as vascular dissection or spasm, and the rate of restenosis is high [1]. In 1982, Choy et al. [2,3] reported the possibility of performing coronary angioplasty using a laser beam, i. e., percutaneous transluminal laser coronary angioplasty (PTLCA). Subsequently, various studies on removal of hypertrophic intima at the sites of vascular stenoses using various types of lasers have been performed at numerous institutions. However, vascular perforation and restenosis, which cannot be completely avoided, are the most serious complications caused by laser angioplasty [4–7]. However, hematoporphyrin derivative (HpD) reported by Lipson et al. [8] in 1960 possesses selective tumor affinity and can be employed for localization of malignant tumors [9,10]. Spikes et al. [11] defined photodynamic action as the eradication or injury of organisms,

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cells, and viruses, or the chemical degradation of molecules, by photoradiation with light in the presence of a photosensitive substance and oxygen molecules. Spears et al. [12] photoradiated the aortae of atherosclerotic rabbits with ultraviolet light following the administration of HpD and verified that HpD fluorescence was localized in the hypertrophic intima of the atherosclerotic lesions. Therefore, it is presumed that if HpD was accumulated in atherosclerotic lesions and if the cytocidal effect of PDT lay in its cell oxidizing action, it might be possible to develop a new therapeutic method for atherosclerosis using HpD with photodynamic effects. Thus we examined the effects of PDT with various concentrations of HpD on the hypertrophic intima of atherosclerotic blood vessels and possibility of safely making atherosclerotic stenotic foci regress and be recanalized, using a low energy laser beam to avoid vascular perforation.

MATERIALS AND METHODS

Animal Preparation

Twenty female Japanese white rabbits (mean body weight 3 kg) were anesthetized intravenously with 30 mg/kg pentobarbital. After the right fermoral artery was exposed and incised under direct visual observation, a No. 4 French Fogarty balloon catheter was inserted and advanced in a retrograde direction for ~25 cm toward the aorta. The balloon was then inflated and withdrawn three times, scratching the intima of the aorta. The catheter was removed, and the femoral artery was ligated. The rabbits were then fed a 0.2% cholesterol diet with 10% peanut oil for 4 weeks to induce atherosclerosis of the aorta.

Laser Delivery Systems

The laser transmission catheter was a lateral direction fiber with semicercumferential photoradiation (YF-60s, Fuji Photo Optical Co., Tokyo, Japan). The delivery catheter consists of a 1,500 μm quartz laser fiber and transmits the beam of an argon-dye laser (Aurora, Heraeus Laser Sonics, CA) with a wavelength of 630 nm at an output power of 200 mW for 10 minutes or 400 mw for 5 minutes (120J/cm^2). Power was measured before and after treatment with a power meter.

Experiment 1

Six of the atherosclerotic rabbits were intravenously given 5 mg/kg of HpD (Pharmacy Department, Queen Elizabeth Hospital, Woodville, Australia) and designated as group A (n = 6). Another group of four rabbits, not treated with HpD, was designated as group B (n = 4). Twenty-four hours after administration of HpD, these rabbits were anesthetized with pentobarbital; then, the peritoneum was detached from the left dorsal portion of the peritoneal cavity. Exposing the vascular segment from the left femoral artery to the aorta, the left femoral artery was incised and a laser catheter with a lateral direction fiber was inserted into the blood flow of the aorta, and two intraluminal sites per rabbit were photoradiated with an argon-dye laser beam of wavelength 630 nm at an output power of 200 mW for 10 minutes. The laser transmission fiber was in contact with the intima. The adventitia of the photoradiated site was marked with black ink for identification. Three rabbits in group A and two rabbits in group B were sacrificed immediately after (day 0) photoradiation and designated as the A 0 group (n = 3) and the B 0 group (n = 2), respectively. The remaining three rabbits in group A and two rabbits in group B were fed a 0.2% cholesterol diet for a further 7 days following photoradiation and then were sacrificed and designated as group A 7 (n = 3) and group B 7 (n = 2). The photoradiated and nonphotoradiated arterial segments were excised, fixed in paraformaldehyde, and glutaraldehyde, and embedded in paraffin. Then, we cut 10-μm-thick cross sections, stained them with hematoxylin and eosin (HE) and elastica- van Gieson (EVG), and examined them by light microscopy (BH-2, Olympus Co., Tokyo). Fresh frozen sections of nonphotoradiated sites of the A 0 and B 0 groups were examined by fluorescence microscopy (AH-2, Olympus) to ascertain the state of selective concentration of HpD in the atheromatous lesions.

Experiment 2

Using the same experimental setup as that of experiment 1, photoradiation by the argon-dye laser was performed at an output power of 400 mW for 5 minutes. Again, among the six rabbits given HpD, three were sacrificed immediately after photoradiation (group C 0, n = 3), whereas the remaining three were sacrificed 7 days after photoradiation (group C 7, n = 3). Likewise, among the four rabbits not treated with HpD, two were sacrificed immediately after photoradiation (group D 0, n = 2) and the remaining two were sacrificed 7 days after photoradiation (group D 7, n = 2) (Fig. 1).

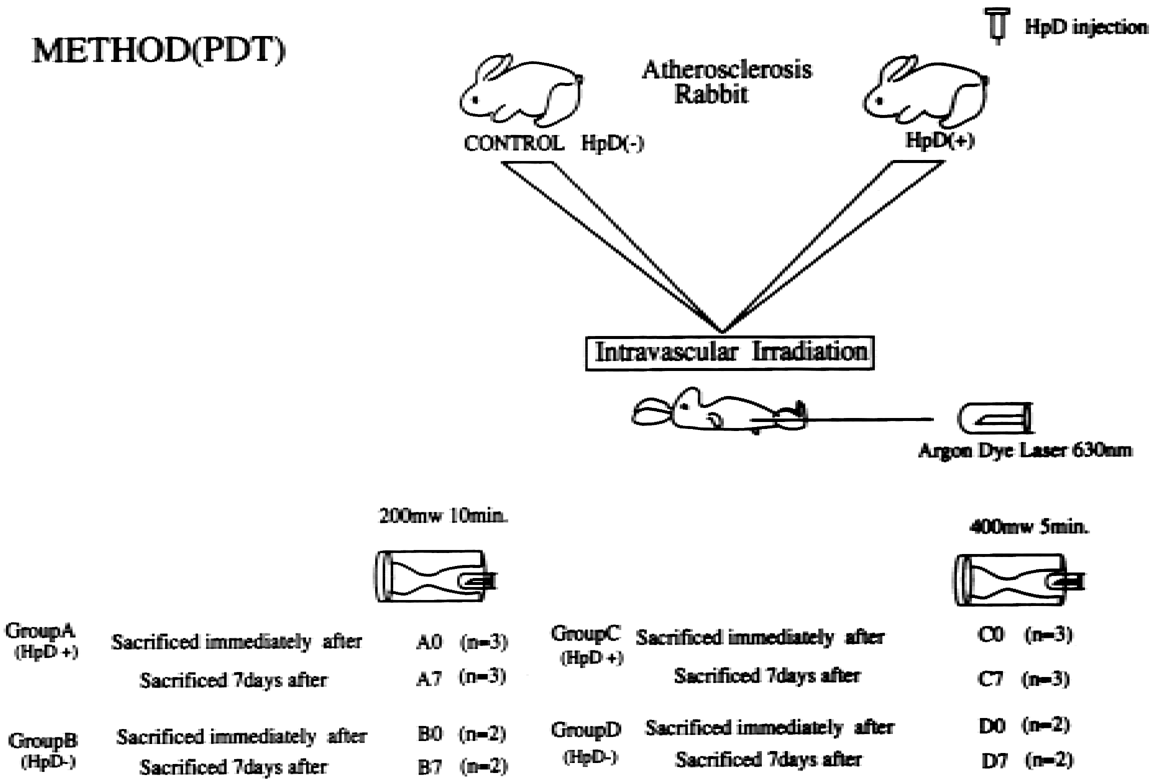

Fig. 1. Experimental method.

Statistics

The intimal thickness of group A 7, C 7 (PDT group) and group B 7, D 7 (laser only group) were expressed in terms of intima, media ratio (I/M ratio). Results are presented as means ± S.D. The Mann-Whitney U test was used to compare the two groups, and P values were considered significant at or below .05.

RESULTS

Atherosclerosis

Figure 2 shows the histological findings in the abdominal aorta of rabbits fed a 0.2% cholesterol diet for 4 weeks following endothelial scratching by the balloon catheter. The intima was hypertrophic all around the lumen, and atherosclerotic findings were pronounced.

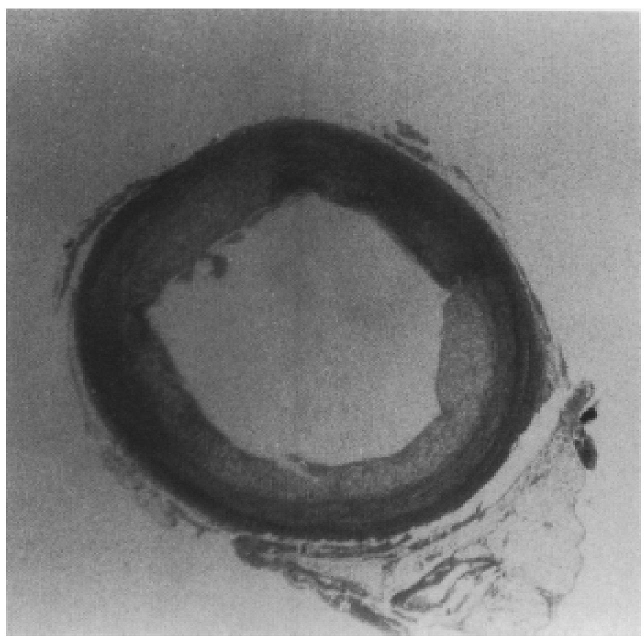

Fig. 2. Photomicrograph of a cross section of an abdominal aorta of a rabbit fed a 0.2% cholesterol diet for 4 weeks following endothelial scratching by the balloon catheter. The intima is hypertrophic all around the lumen, and atherosclerotic findings are pronounced. EVG staining; magnification ×10.

Fluorescent Analysis

The localization of HpD at the sites of the atheromatous lesions in a specimen from the A 0 group is shown in Figure 3a. Fluorescence microscopy revealed the presence of red fluorescence, indicating the presence of HpD in the intima of the thickened area. However, this fluorescence

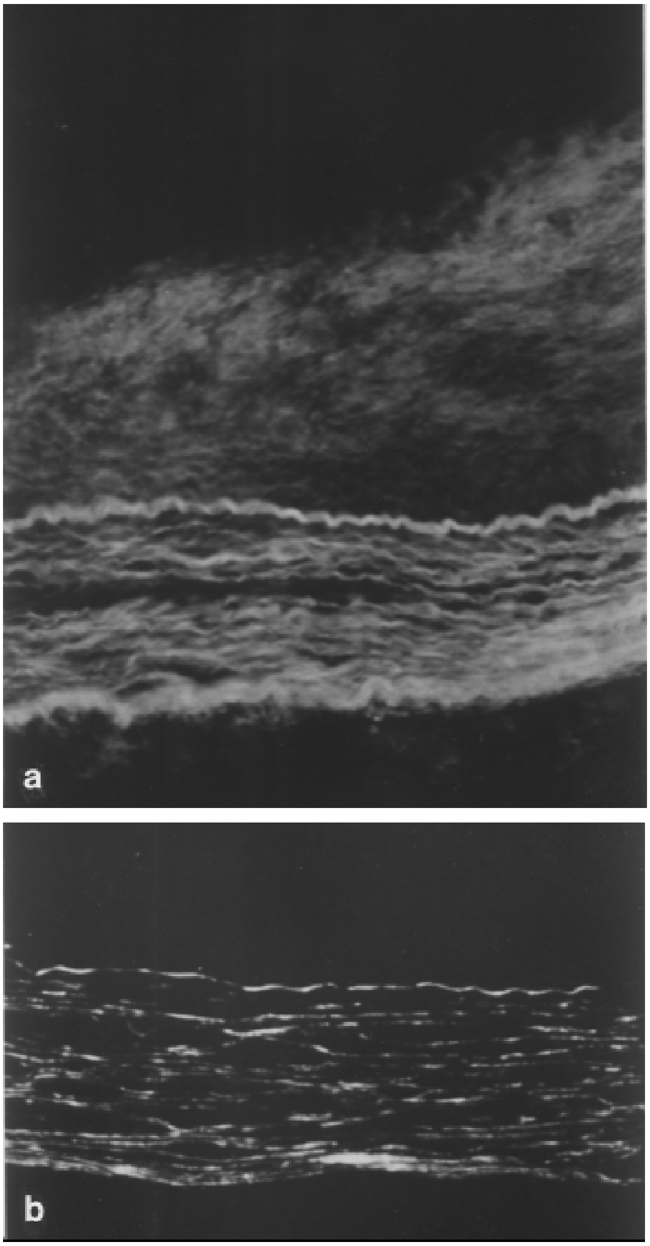

Fig. 3. (**a**) Fluorescence photomicrograph of the cross-section of an abdominal aorta of an A 0 rabbit. It reveals the presence of red fluorescence, indicating the presence of HpD in the thickened area of intima. (**b**) Fluorescence photomicrograph of a specimen from group B 0, showing the absence of the localized concentration of HpD seen in a.

was not seen in the media or adventitia. The intensity of the fluorescence progressively diminished towards the media. Figure 3b shows a fluorescence photomicrograph of a specimen from group B 0, showing the absence of the localized concentration of HpD seen in Figure 3a.

Photodynamic Therapy

Figure 4 shows representative findings obtained by HE staining of the aortic intima at a laser-photoradiated site in a specimen from group A 0. The endothelial cells had completely disappeared, and migration of eosinophils and monocytes could be observed on the intimal surface. However, despite these changes, no signs of thermal degradation effects such as carbonization or vaporization were observed. Representative HE stain findings at a site of laser-photoradiation in a specimen from group B 0 are shown in Figure 5. No abnormalities were recognized in the endothelium, intima, media, or adventitia, indicating that the laser energy manifested no appreciable effects in this case. Figure 6 shows HE findings of a group A 7 specimen showing a loss of intimal tissue. However, no changes are recognized in the media or adventitia. Moreover, endothelial loss was only at the laser photoradiated site, whereas endothelial cells remained at the nonphotoradiated site. In group B 7, as in group B 0, no abnormalities were observed at the photoradiated sites. Figure 7 shows the results of HE and EVG staining in specimens from group C 7. Although intimal hypertrophy resulting from atherosclerotic changes was evident almost around the entire circumference of the vascular lumen, intimal atrophy was observed at the site of laser photoradiation. Magnified images of the same site are shown in Figure 8a (HE stained) and Figure 8b (EVG stained). Figure 8a shows a loss of intimal tissue in the intima. However, no changes were recognized in the media or adventitia. In Figure 8b, in a zone coinciding with the site of laser photoradiation on the luminal side of the internal elastic lamina, the intima was observed to have disappeared, but no thermal effects were recognized. Figure 9 shows an HE stained specimen from group D 7, showing no changes in the thickened intima, intimal cells or endothelial cells.

I/M ratio

The I/M ratio of PDT groups was 0.043 ± 0.017, whereas that of the laser only groups was 0.535 ± 0.264. Significance was recognized at a level of 99% by the Mann-Whitney U test (Fig. 10).

DISCUSSION

Mechanism of PDT

Upon photoradiation with a low-energy laser beam, HpD concentrated in the atherosclerotic le-

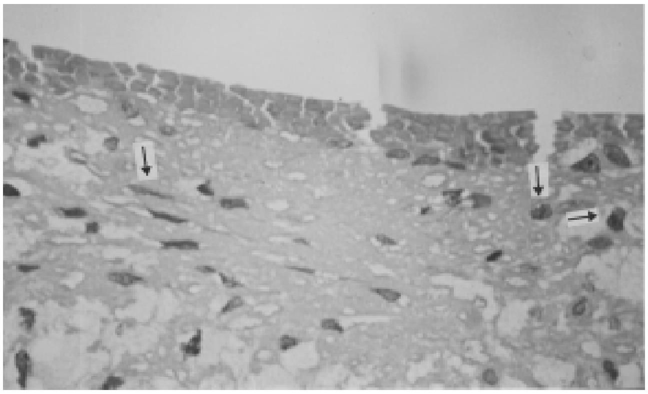

Fig. 4. Photomicrograph of the cross-section of the abdominal aorta at a laser photoradiated site in a specimen from group A 0. The endothelial cells have completely disappeared, and migration of eosinophils, monocytes, and inflammatory cells (arrows) are observed on the intimal surface. However, despite these changes, no signs of thermal degradation effects such as carbonization or vaporization are observed. HE staining × 400.

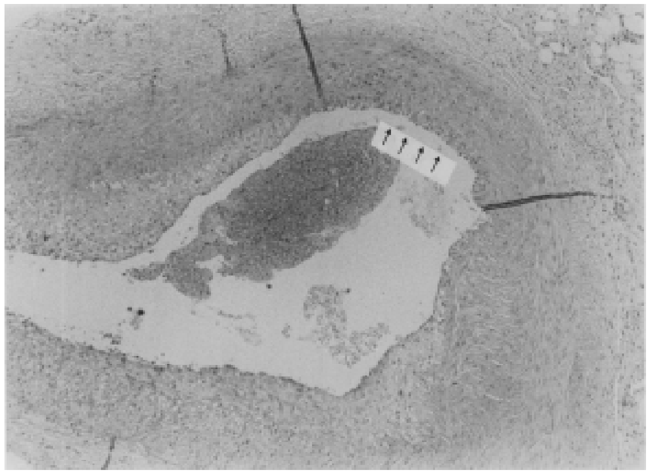

Fig. 6. Photomicrograph of the cross section of a group A 7 specimen shows a loss of intimal tissue at a laser photoradiated site (arrows). However, no changes are recognized in the media or adventitia. HE staining × 40.

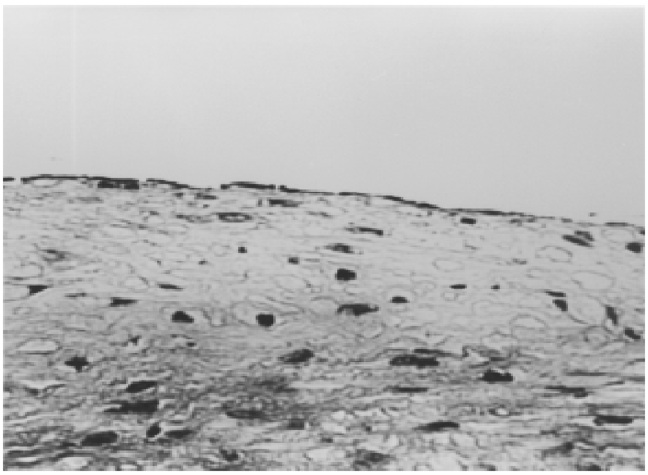

Fig. 5. Photomicrograph of the cross section of the abdominal aorta at a laser photoradiated site in a specimen from group B 0. No abnormalities are recognized in the endothelium, intima, media, or adventitia. HE staining × 400.

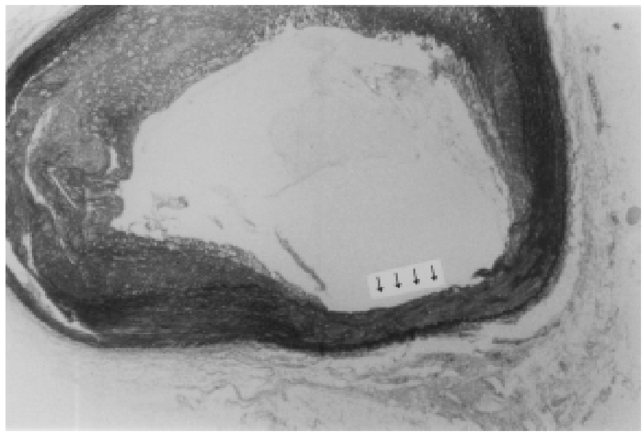

Fig. 7. Photomicrograph of a cross section of a group C 7 rabbit. Although intimal hypertrophy resulting from atherosclerotic changes is evident almost entirely around the circumference of the vascular lumen, intimal atrophy is observed at the site of laser photoradiation (arrows). EVG staining × 20.

sion is excited from the ground state to the singlet state, undergoes a further transition to the triplet state, and then reverts to the ground state. The energy produced by the return to the ground state from the triplet state is transferred to a triplet oxygen molecule within the atheromatous lesion, thereby transforming the oxygen molecule to the singlet state, and the potent cytocidal action of the singlet oxygen induces necrosis and regression of the atheromatous tissue [13].

HpD Accumulation

Although this study verified the concentration of HpD in the atherosclerotic lesions of the rabbits, the mechanism of this selective concentration in atherosclerotic lesions and the precise site of concentration have not been clarified. However, concerning atherogenesis and restenosis, mounting evidence supports the concept that migration of smooth muscle cells (SMC) across the vascular wall is important in the initiation of myointimal thickening and plaque development [14]. Other PDT studies demonstrated that PDT is effective at the cell culture level with respect to medial SMC of rat aortae. Cultivated SMC obtained from both atherosclerotic and nonathero-

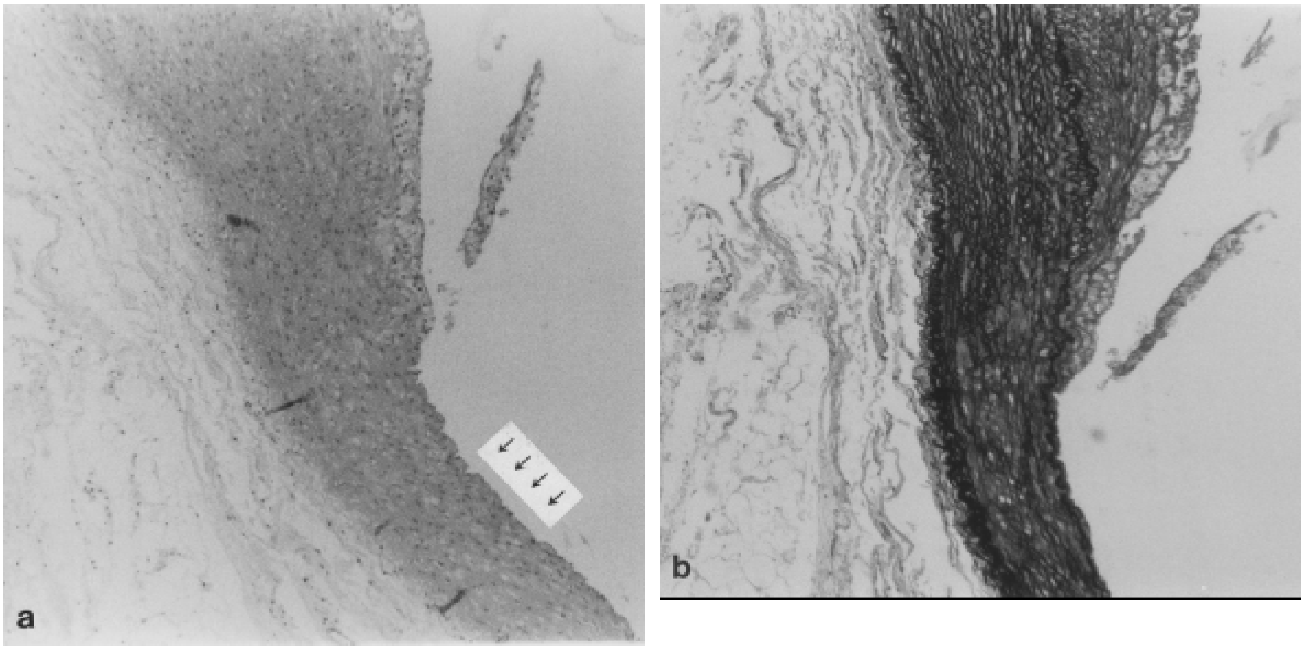

Fig. 8. (**a**) Photomicrograph of magnified images of the same site shown in Figure 7 showing a loss of intimal tissue at the laser photoradiated site. However, no changes are recognized in the media or adventitia (arrows). HE staining × 40 (**b**) Photomicrograph of magnified images of the same site shown in Figure 7. In a zone coinciding with the site of laser photoradiation the intima is observed to have disappeared on the luminal side of the internal elastic lamina, whereas no thermal effects are recognized. EVG staining × 40.

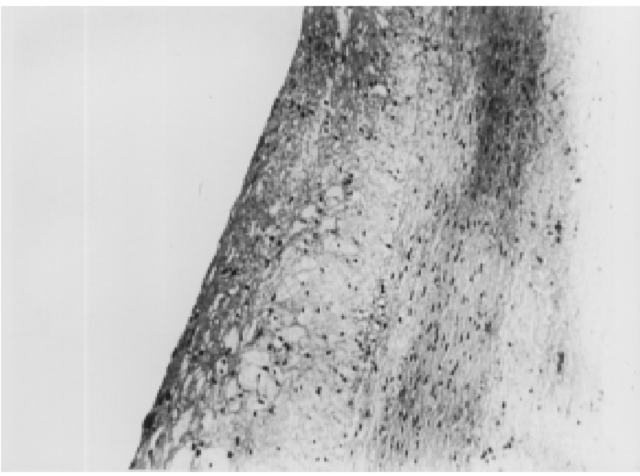

Fig. 9. Photomicrograph of specimen from group D 7, showing no changes in the thickened intima, intimal cells, or endothelial cells. HE staining × 100.

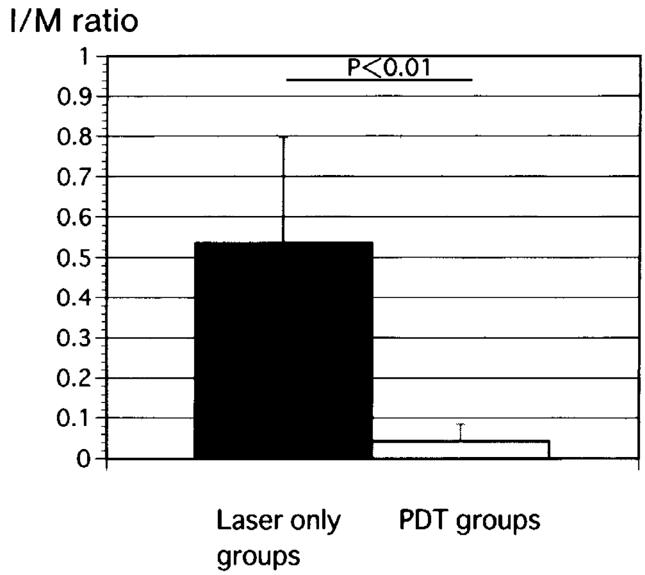

Fig. 10. Bar graph showing the treated intima site, media ratio of the laser-only groups and PDT groups. Data are expressed as means ± SD. Laser-only groups n = 4; 8 sites, PDT groups n = 6; 12 sites.

sclerotic sites in human tibial arteries and aortae were treated by PDT. It was reported that there was comparatively more effect against SMC obtained from atherosclerotic lesions than those from nonatherosclerotic sites [15,16]. Thus it is suggested that HpD accumulation is related to the synthetic phenotype of SMC [17].

Laser Ablation

Various techniques have been contemplated for the application of laser beams in the treat-

ment of atherosclerotic lesions, especially coronary artery lesions. However, due to the special morphological characteristics of such lesions, the appropriate selection of the type and output of the laser as well as the accurate identification of the site to be photoradiated are difficult. Watari et al. [18] reported that atherosclerotic lesions can be located using HpD, applying low energy laser radiation and measuring the emitted fluorescence. This can permit more accurate evaluation of the atherosclerotic lesions. Although excimer lasers are in clinical use, a high rate of restenosis and other complications accompanying the use of such lasers have been reported [5]. Beam calibers exceeding the fiber diameter cannot be obtained with excimer lasers, but increasing the diameter of the fiber impedes manipulation and entails greater risk of complications. It is therefore necessary to develop safer and more effective methods for laser photoradiation.

PDT Studies

Nakajima [19] demonstrated in in vivo studies with respect to rabbit atherosclerotic lesions that PDT can be performed by applying laser radiation from an extravascular position and suggested that PDT is effective for atherosclerotic lesions in rabbits. In the present study, a laser fiber for lateral semicircumferential photoradiation was used to apply laser radiation from an intravascular position in order to simulate clinical conditions as closely as possible. The absorption spectrum of HpD has a Soret band at 405 nm and Q bands at 488 nm, 514 nm, and 630 nm. A 630 nm argon-dye laser was used in the study, because laser photoradiation was performed within the bloodstream, and hemoglobin possesses an absorption band at 490 nm, which can absorb laser light, and because the tissue penetration depth of this light is comparatively shallow. The radiation times and outputs used were 10 minutes at 200 mW, 5 minutes at 400 mW. Necrosis and eradication of the photoradiated tissue was observed after a 200 mW, 10-minute dose. However, the maintenance of a laser fiber within a coronary artery for a long period of 10 minutes was presumed to be hazardous. On the basis of PDT studies with cultured cancer cells, Kuwabara et al. [20] stated that PDT displays cytocidal effects with survival rates inversely dependent upon photoradiation time, intensity, and photosensitizer concentration. Assuming that this is also applicable to PDT with respect to atherosclerotic lesions, a similar set of intravascular rabbit experiments was performed, increasing the intensity of photoradiation by raising the output power to 400 mW and shortening the time to 5 minutes. The results, as indicated in Figure 7, demonstrated that necrotic disintegration of the intima occurred at sites coinciding with the locations of the atherosclerotic lesions, whereas no abnormalities were observed in the elastic lamina, media, or adventitia. This indicated that the thermal effects due to the elevation of output power from 200 mW to 400 mW were slight and suggested that the cytocidal effects of PDT were confined to the portions of the intima with uptake of HpD. This indicated that PDT could be safely and effectively performed with a photoradiation period of 5 minutes and an output ranging from 200–400 mW. Furthermore, the endothelial cells disappeared over an area coinciding with the site of photoradiation, but unlike PTCA, no abnormalities were observed in the media or adventitia. Based on the fact that no findings indicating thermal degradation, such as carbonization, etc., were recognized, no significant heat effects were manifested at the energy level required for PDT under the conditions of this study. Furthermore, no vascular spasm or perforation were noted in any case. In addition, the mechanism of restenosis may be based on the stimulation of medial SMC proliferation [21], but PDT did not stimulate the media or adventitia, suggesting that PDT might cause less restenosis than PTCA.

Limitations of This Study

The lateral photoradiation type laser fiber employed in the present study is still not adequate since only one side of a circumferential type lesion can be photoradiated at one time. In completely occluded cases the fiber would be unable to penetrate the site of the lesion and therefore would be inapplicable. Accordingly, combined use of the present and other types of laser was contemplated as a means of solving this problem in completely occluded cases. Oike et al. [22] showed that atherosclerotic intima that has taken up HpD can be removed with low laser photoradiation, but that without HpD the atherosclerotic intima is unaffected. This phenomenon was attributed to the elevation of sensitivity to the laser light by HpD. Based on this, another type of laser could be employed to create an aperture with a diameter approximately equal to that of the PDT fiber in an atherosclerotic lesion, which has taken up HpD; then the aperture could be further enlarged by applying PDT to this site. To achieve

this, a diffuse type of laser fiber capable of photoradiating the entire circumference of a vascular lumen is currently being used in our laboratory and its efficacy is being evaluated. Regarding the selective concentration of HpD in human atherosclerotic lesions, Spokojny et al. [23–25] have verified that if excised arteries are incubated with HpD, the HpD concentrates at atherosclerotic sites in the arteries, thus indicating the possibility that HpD would also concentrate in atherosclerotic lesions of human arteries in vivo. However, even in such cases the patient would require protection from exposure to light for ~1–2 weeks following administration, owing to the light sensitizing effects of this substance. The use of other varieties of photosensitive substances for the same purpose is currently being studied in our laboratory.

CONCLUSION

The photosensitive substance HpD, which is reported to concentrate at the sites of atherosclerotic lesions, was investigated by animal experiments, and the concentration of HpD in the atherosclerotic lesions of rabbit arteries was verified by fluorescence microscopy. The possibility of utilizing PDT to induce regression and cure atherosclerotic lesions was investigated by applying intravascular laser photoradiation to atherosclerotized rabbits in vivo. A lateral 180° radiation-type laser probe was introduced via the femoral artery after intravenous administration of HpD, and photoradiation was applied with an argon-dye laser at an output of 200 mW for 10 minutes and 400 mW for 5 minutes. The rabbits were divided into groups sacrificed immediately after photoradiation as well as those reared on a cholesterol-rich diet for a further 7 days after photoradiation.

1. The selective concentration of HpD in atherosclerotic lesions in rabbits was verified by fluorescence microscopy.

2. In a control group, which was not given HpD, no changes in the intima were observed after photoradiation at 200 mW for 10 minutes or 400 mw for 5 minutes.

3. In the group treated with HpD and sacrificed immediately after photoradiation at 200 mW for 10 minutes and 400 mw for 5 minutes, the cellular component of the atherosclerotic sites in the intima displayed traumatic findings such as migration of neutrophils and platelets. However, no signs of thermal degradation were observed.

4. In the group treated with HpD and sacrificed 1 week after photoradiation at 200 mW for 10 minutes and 400 mw for 5 minutes, all the intimal cells at the site of photoradiation were eradicated or necrotic, compared to the nonphotoradiated area. The results obtained verified that HpD concentrates in atherosclerotic lesions in rabbit arteries and that effective treatment of such lesions by PDT is possible using an argon-dye laser for a period of 5–10 minutes at an output in the range from 200–400 mW. These experimental results indicate that PDT has great potential for the treatment of atherosclerosis in ischemic heart disease patients.

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